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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/880,654	06/13/2001	Leanna M. Levine	2842/3	7335

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Pharmacia Corporation
Corporate Patent Department
800 North Lindbergh Blvd.
Mail Zone O4E
St. Louis, MO 63167

EXAMINER	
WINKLER, ULRIKE	
ART UNIT	PAPER NUMBER
1648	6

DATE MAILED: 11/19/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/880,654	LEVINE ET AL.	
	Examin r	Art Unit	
	Ulrike Winkler, Ph.D.	1648	

-- The MAILING DATE of this communicati n appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *September 26, 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's election without traverse of Group I in Paper No. 5 is acknowledged. Claims 1-11 are under consideration in the instant office action.

Information Disclosure Statement

An initialed and dated copy of Applicant's IDS form 1449, Paper No. 3, is attached to the instant Office Action.

Sequence listing

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825) before the application can be examined under 35 U.S.C. §§ 131 and 132.

Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a). Direct the reply to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the reply.

Note: Applicants have provided a CRF in the parent application 09/327170. Applicant may request that the Sequence Listing be transferred from that case. Applicant's will need to provide a separate paper copy of the "Sequence Listing".

A reply to a notice to comply with the sequence rules should NOT be sent to the 20231 zip code address for the United States Patent and Trademark Office.

Please direct all replies to the United States Patent and Trademark Office via one (1) of the following:

1. Electronically submitted through EFS-Bio (**<http://www.uspto.gov/ebc/efs/downloads/documents.htm>**, EFS Submission User Manual - ePAVE)

2. Mailed to:
U.S. Patent and Trademark Office
Box Sequence, P.O. Box 2327
Arlington, VA 22202

3. Mailed by Federal Express, United Parcel Service or other delivery service to:
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Arlington, Virginia 22202

4. Hand Carried directly to the Customer Window at:
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Arlington, Virginia 22202

Drawings

The drawings are objected to, please see Notice of Draftsperson's Review attached to the instant Office Action. Correction is required.

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

1. Correction of Informalities -- 37 CFR 1.85

New corrected drawings must be filed with the changes incorporated therein. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings **MUST** be filed within the **THREE MONTH** shortened statutory period set for reply in the "Notice of Allowability." Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136 for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

2. Corrections other than Informalities Noted by Draftsperson on form PTO-948.

All changes to the drawings, other than informalities noted by the Draftsperson, **MUST** be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings **MUST** be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

Timing of Corrections

Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.185(a). Failure to take corrective action within the set (or extended) period will result in **ABANDONMENT** of the application.

Claim Objections

Claims 4, 6, 8, 9 and 10 objected to because of the following informalities: the claims use abbreviations such as "DANSYL, DABCYL, EDANS, DTAF, HIV, HCMV, MCMV "; the compounds should be spelled out before the first use of each abbreviation. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 10 recites the limitation "Abu" in the claim, according to the abbreviations allowed see MPEP 2422 the abbreviation Abu is 2-Aminobuteric acid. There is insufficient antecedent basis for this limitation in the claim since claim 3 does not recite 2-aminobuteric acid as one of the enumerated groups. Amending the claim so it is depends from claim 2 would obviate this rejection as Abu is an aminoalkylcarboxylic acid.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 10 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The specification does not provide sufficient description of a protease that is capable of cleaving the compound in claim 10 and produce a product with the sequence Biotin-Gly-Val-Val-Asn-Ala-Arg-Ser-Ala-Leu-Arg-Lys-(DTAF) shown in claim 10. The specification is inconsistent in its use of the sequence identifier SEQ ID NO:3, the compound depicted in example 1 (page 16) and on page 17, lines 1-2 are different from the compounds identified in claim 10 as SEQ ID NO:3 and figures 1-3 of the specification. The specification does not

provide a written description of a protease that is able to cleavage between the Arg-Ser as set forth in the sequence of SEQ ID NO:3 in claim 10. Therefore, there is insufficient written description for a protease that can cleave the compound of SEQ ID NO:3 in claim 10.

Claim 10 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant claim is evaluated for scope of enablement based on the Wands analysis. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731,8 USPQ2d 1400 (Fed.Circ.1988) as follows: (1) the nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the relative skill of those in the art, and (8) the breadth of the claims. The Wands factor analysis, such an analysis does not need to specifically enumerate (points 1-8) but only needs to have a select few of the factors discussed in a rejection.

The nature of the invention is a compound that is used in measuring the activity of a protease. The specification discloses a human cytomegalovirus protease, the state of the prior art is such that the protease cleavage sites for human cytomegalovirus and other herpesviruses are known (see table 1 and 3, Welch et al. PNAS 1991). The prior art has determined the protease cleavage site consensus sequence, which is V/L-X-A↓S/V. The predictability in the art high when it comes to preferred amino acid in the cleavage site. Changing the preferred alanine to an arginine in the substrate cleavage site would lead the ordinary artisan to predict that the substrate

would not work for a herpesvirus protease because of the highly charged amino acid argenine. There are no working examples of proteases that cleaves the compound set forth in claim 10 as SEQ ID NO:3. Without the presence of working examples one of ordinary skill in that art would not be able to predict what proteases might cleave the compound set forth in claim 10 as SEQ ID NO:3. Therefore, the compound is not enabled as a substrate for the disclosed methods.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5, 7, 8 and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Heath et al. (U.S. Pat. No. 5,235,039).

The instant invention is drawn to a method of determining the activity of a compound, the compound contains a fluorescent group on one side of an amino acid sequence and a binding group at the opposite end of the amino acid sequence. The compound may or may not contain spacer molecules between the fluorescent group and the amino acid or between the binding group and the amino acid. The instant invention is also directed at identifying compounds that inhibit the activity of a protease. The method comprises steps such as incubating the mixture of protease and substrate and measuring fluorescence polarization of the mixture. When measuring the activity of an inhibitor the inhibitor is added into the mixture as well.

> MPEP 2111.03 The transitional term "comprising", which is synonymous with "including," "containing," or "characterized by," is inclusive or open-ended and does not exclude additional, unrecited elements or method steps. See, e.g., *Genentech, Inc. v. Chiron Corp.*, 112 F.3d 495, 501, 42 USPQ2d 1608, 1613 (Fed. Cir. 1997) ("Comprising" is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim.); *Moleculon Research Corp. v. CBS*, Inc., 793 F.2d 1261, 229 USPQ 805 (Fed. Cir. 1986); *In re Baxter*, 656 F.2d 679, 686, 210 USPQ 795, 803 (CCPA 1981); *Ex parte Davis*, 80 USPQ 448, 450 (Bd. App. 1948) ("comprising" leaves "the claim open for the inclusion of unspecified ingredients even in major amounts").

In view of the comprising language used in the claim additional steps are permitted as well.

Heath et al. discloses a method for rapidly measuring the amount of a hydrolytic enzyme generated or released by a proenzyme in multiple samples wherein the substrate for said enzyme comprises recognition sites on both sides of the cleavage site (see column 11, lines 6-11). The reference additionally discloses an assay method for determining inhibitory activity of test compounds which comprises the steps (see column 11, lines 45 to column 12, line 5): a) incubating in the presence of a test compound a protease and a substrate for said protease wherein said substrate is bonded on one side of the cleavage site with a resin-binding compound and on the opposite side with a reporter molecule; b) transferring the incubation solutions from each well of the multiple-well plate to a second multiple well plate wherein the wells have an upper and lower chamber separated by a porous membrane, wherein each upper chamber of said wells contains a solution or suspension of resin beads capable of irreversible binding to said resin-binding compound bonded to the substrate and wherein the size of said resin beads precludes passage of the bound substrate, or the hydrolyzed portion thereof bonded to the resin, through said membrane; c) filtering and washing each of said two-chambered wells; and d) measuring the emission in each well of said second plate. It will be recognized by those in the art that the conditions of incubation i.e. time, temperature and pH will vary somewhat depending

upon the particular protease-substrate reaction. Typically, standard buffers are employed in the incubations which are in general carried out at mild temperatures of about room temperature to about 40°C. In transferring the incubation solutions to the wells in the second multiple well plate the incubation mixture can be diluted with a suitable buffer to provide a desirable concentration. The preferred resin-binding compound of the invention is biotin. A preferred reporter compound is a fluorescence marking compound such as that formed with the substrate and fluorescein isothiocyanate. Preferred resin beads are polystyrene beads coated with avidin which are commercially available.

The compound used in the method comprises a resin binding compound, such as biotin to one side of a scissile bond of the substrate and a reporter molecule such as a fluorescence marker on the opposite side of the scissile bond (see example 1, column 17). The reference discloses the compound according to Formula 1: Z= biotin, m=1, W=Gly, X= 9 amino acids, n=0, V =glycine, 4-aminobutyric acid, 5-aminopentanoic acid, 6-aminocaproic acid or 7-aminoheptanoic acid, Y= FITC (fluorescein isothiocyanate). The reference discloses carrying out the assay method to discover and study inhibitors of HIV-1 protease. Recent studies show that inhibition of the HIV-1 protease blocks production of infectious virus. The natural substrate of this protease is the gag-pol precursor protein which is cleaved into four core proteins and the essential enzymes HIV-1 protease, reverse transcriptase, ribonuclease H, and endonuclease. One consensus sequence for this cleavage is (Ser/Thr)-Xaa-Xaa-(Tyr/Phe)-Pro in which cleavage occurs N terminal to Pro. In this embodiment of the invention a decapeptide analog of the natural scissile region is employed to screen for inhibitors of the HIV-1 protease. The decapeptide is represented by the formula Gly-Ser-Gln-Asn-Tyr-Pro-Ile-Val-Gly-Lys-OH and is cleaved by the protease between the Tyr-

Pro portion. For use in the assay the N-terminus of the decapeptide is coupled with biotin and the .epsilon.-amino group of the C-terminal lysine is reacted with the fluorescent marker, fluorescein isothiocyanate to provide the modified peptide represented by the formula N.sup..alpha. -Biotin-Gly-Ser-Gln-Asn-Tyr-Pro-lle-Val-Gly-Lys-N.sup..epsilon. -(FITC)-OH (see column 8, lines 40-62). Therefore, the instant invention is anticipated by Heath et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-11 are rejected under 35 U.S.C. 103(a) as being obvious over Heath et al. (U.S. Pat. No. 5,235,039) in view of Welch et al. (PNAS 1991) or Blakeslee et al. (Journal of Immunological Methods, 1976).

The instant invention is drawn to a method of determining the activity of a compound, the compound contains a fluorescent group on one side of an amino acid sequence and a binding group at the opposite end of the amino acid sequence. The compound may or may not contain spacer molecules between the fluorescent group and the amino acid or between the binding group and the amino acid. The instant invention is also directed at identifying compounds that inhibit the activity of a protease. The method comprises steps such as incubating the mixture of protease and substrate and measuring fluorescence polarization of the mixture. When measuring the activity of an inhibitor the inhibitor is added into the mixture as well. The specific compound set forth in claim 10 is biotin-γ-Ser-Gln-Asn-Tyr-Pro-Ile-Val-Gln-Lys-DTAF.

Heath et al. teaches a method for rapidly measuring the amount of a hydrolytic enzyme generated or released by a proenzyme in multiple samples wherein the substrate for said enzyme comprises recognition sites on both sides of the cleavage site (see column 11, lines 6-11 and discussion above). The reference additionally discloses an assay method for determining inhibitory activity of test compounds which comprises the steps (see column 11, lines 45 to column 12, line 5). (see above). The reference teaches a compound that comprises bonding a resin binding compound, such as biotin to one side of a scissile bond of the substrate and a reporter molecule such as a fluorescence marker on the opposite side of the scissile bond (see example 1, column 17). The reference discloses the compound according to Formula 1 in the following way. Z= biotin, m=1, W=Gly, X= 9 amino acids, n=0, W=glycine, 4-aminobutyric acid, 5-aminopentanoic acid, 6-aminocaproic acid or 7-aminoheptanoic acid, Y= FITC (fluorescein isothiocyanate). Example 1 teaches the compound, biotin-Gly-Ser-Gln-Asn-Tyr-Pro-Ile-Val-Gly-Lys-FITC. The reference does not teach a method using the compound biotin-γ-

Abu-Gly-Ser-Gln-Asn-Tyr-Pro-Ile-Val-Gly-Lys-DTAF. The reference also does not teach herpesvirus protease cleavage sites.

Welch et al. teaches substrates for herpes virus protease, the reference does not teach attaching a flourophore on one end of the peptide sequence and a binding agent at the other end of the peptide sequence.

Blakeslee et al. teaches the conjugation of DTAF to an antibody. The reference teaches that DTAF and FITC have nearly identical properties. However, DTAF is superior to FITV in regards to cost, purity and stability. The reference does not teach using DTAF in a protease substrate.

It would have been obvious to one of ordinary skill in the art at the time the invention was made utilize the substrate construction as taught by Heath et al. and apply them to the peptide substrates of taught by Welch et al. One would have been motivated to do this in order to develop a fast inhibition assay for herpes virus proteases in order to have an easy screening assay. Optimizing experimental conditions, including the addition of spaces between the amino acid and the binding group or fluorescing group, choosing the fluorescing group so that it minimizes quenching and optimizes signal output, falls within the skills of an ordinary artisan. Blakeslee et al. teaches that DTAF and FITC have identical properties, however, because of the lower cost involved with DTAF one having ordinary skill in the art would have been motivated to substitute DTAF for FITC in the substrate taught by Heath et al. Therefore, the instant invention is obvious over Heath et al. in view of Welch et al. or Blakeslee et al.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ulrike Winkler, Ph.D. whose telephone number is 703-308-8294. The examiner can normally be reached M-F, 8:30 am - 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached at 703-308-4027.

The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for informal communications use 703-308-4426.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Ulrike Winkler, Ph.D. 11/18/02

Notice to Comply	Application No.	Applicant(s)	
	09/880,654	LEVINE ET AL.	
	Examiner	Art Unit	
	Ulrike Winkler, Ph.D.	1648	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☒ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

X 7. Other: Applicant should follow the format of the attached sample statement to request that the CRF filed in the parent application be used to create a CRF in this application.

Applicant Must Provide:

☐ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
For CRF Submission Help, call (703) 308-4212
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